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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	10

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/021,906	CHEE ET AL.
	Examiner	**Art Unit**
	Teresa E Strzelecka	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-43 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.

4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to an amendment filed on August 8, 2003. Claims 27-42 were previously pending. Applicants amended claims 27, 28, 37, 38 and added new claim 43. Claims 27-43 are pending and will be examined.

2. Applicants' amendments and arguments overcame the following rejections: rejection of claims 27-29 and 31-42 under 35 U.S.C. 112, first paragraph and rejection of claims 27-29 and 31-42 under 35 U.S.C. 112, second paragraph. The art rejections are maintained for reasons given in the "Response to Arguments" section.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on August 8, 2003 was filed after the mailing date of the first office action on April 8, 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed August 8, 2003 have been fully considered but they are not persuasive.

A) Regarding rejection of claims 27-42 under 35 U.S.C. 102(e) over Fan et al., applicants argue that this rejection is invalid because the benefit of the following priority applications: 60/135,053 (filed May 20, 1999), 60/130,089 (filed April 20, 1999), 60/135,051 (filed May 20, 1999), 60/135,123 (filed May 20, 1999), 60/161,148 (filed October 22, 1999), 60/160,917 (filed October 22, 1999) and 60/160,927 (filed October 22, 1999) should be given to the instant application. However, none of these applications provide priority for Applicants' claimed

invention, which is a method of detecting products of a rolling circle amplification (RCA) reaction. In particular, the following describe contents of these priority applications:

a) 60/135,053 (filed May 20, 1999), entitled "Genotyping Using Microsphere Arrays", teaches detection of mutations using OLA (oligonucleotide ligation assay), Invader technology, competitive probe analysis, pyrosequencing, LCR, CPT (cycling probe technology), PCR, SDA (strand displacement amplification), NASBA (nucleic acid sequence based amplification), and "branched DNA" signal amplification. No RCA is mentioned.

b) 60/130,089 (filed April 20, 1999), entitled "Nucleic Acid Sequencing Using Microsphere Arrays", teaches sequencing of nucleic acids on bead arrays. No RCA is mentioned.

c) 60/135,051 (filed May 20, 1999), entitled "Detection of Nucleic Acid Amplification Reactions of Nucleic Acids Using Bead Arrays for Detection", teaches PCR, SDA, NASBA, CPT, LCR, Invader technology and "branched DNA" signal amplification. No RCA is mentioned.

d) 60/135,123 (filed May 20, 1999), entitled "Addressing Arrays Using Sequence Specific Adapters", teaches using adapters for capturing nucleic acids onto arrays. No RCA is mentioned.

e) 60/161,148 (filed October 22, 1999), "Detection of Nucleic Acid Amplification Using Bead Arrays", teaches PCR, SDA, NASBA, CPT, LCR, Invader technology and "branched DNA" signal amplification. No RCA is mentioned.

f) 60/160,917 (filed October 22, 1999), entitled "Addressing Arrays Using Sequence Specific Adapters", teaches using adapters for capturing nucleic acids onto arrays, and PCR,

SDA, NASBA, CPT, LCR, Invader technology and "branched DNA" signal amplification. No RCA is mentioned.

g) 60/160,927 (filed October 22, 1999), "Nucleic Acid Sequencing Using Microsphere Arrays", teaches sequencing of nucleic acids on bead arrays. No RCA is mentioned.

Therefore, none of these applications contains any mention of RCA technology. Applicants proceed to argue one specific application, 60/135,053. Applicants argue that the application teaches multiplex PCR, template DNA on solid support (page 19 of the amendment, last two paragraphs), attachment of nucleic acid probes to microspheres distributed on the solid support (page 20 of the amendment, first paragraph), use of capture probes on microsphere microarrays (page 20 of the amendment, second paragraph), use of nucleic acid probes and hybridization for detection of a target sequence (page 20 of the amendment, last paragraph), use of a primer, particularly in LCR, CPT and Invader technologies (page 21 of the amendment, first and second paragraphs). Finally, Applicants argue that "… the entire section entitled "Invention Disclosure Form" provides explicit details for the above methods of detection. Accordingly, <u>the application teaches the elements in steps (a)-(c) of hybridizing a probe or a primer to a target nucleic acid to form a hybridization complex and modifying the probe or primer</u>." (page 21 of the amendment, fourth paragraph), emphasis added.

First, the section entitled "Invention Disclosure Form" does not provide support for RCA, as it teaches the following methods: SBE (single base extension), or minisequencing, OLA, allele-specific PCR and allele-specific hybridization. Furthermore, the crucial difference between RCA and the general methods outlined by Applicants above is the fact that a circular primer, after being hybridized to the target nucleic acid in step (a), is circularized by a ligase in step (b), and the circular probe formed is amplified in step (c). Therefore, while the priority application teaches

OLA and LCR, both of which use two linear probes, which are ligated after being hybridized to a target sequence, these are not circularized, and may not even be further amplified, it does not provide support for RCA.

On page 21, last paragraph, and on page 22, Applicants argue that the priority application specifies different amplication methods. However, RCA is not one of them. On page 23, first paragraph, Applicants state "Further, the '053 application teaches forming a circularized probe as claimed in step (b) of the application as well as teaches amplifying such a probe with a primer to form a concatamer amplicon as is claimed in step (c)." Applicants do not provide information where in the priority application this teaching occurs, and none was found.

Applicants proceed to argue that the application teaches cleavage of concatamer products by pointing to a paragraph which teaches PCR. No concatamers are formed in a PCR reaction. Applicants argue that the application exemplifies ten additional PCR methodologies. None of them provide support for RCA.

Applicants argue that the application provides support for RCA, since it provides support for SDA (page 23 of the amendment, last paragraph), and "... amplification of a circular nucleic acid is a strand displacement amplification methodology." (page 24 of the amendment, first paragraph). This argument is not found persuasive. In SDA, a linear nucleic target is contacted with two primers on the 3' ends of the target, where the primers contain a 5'end which contains a recognition site for a restriction endonuclease, extending the primers with a polymerase in the presence of modified dNTP, nicking the extended strand with the restriction endonuclease and extending from the nick, displacing the first synthesized strand. Therefore, SDA does not provide support for amplification of circular nucleic acids.

Applicants argue that cyclization of nucleic acids were well known in the art, and amplification of plasmids was known more than 14 years before the filing date of the '053 application (page 24 of the amendment, second paragraph). However, this feature alone does not provide support for RCA. Furthermore, if it made RCA obvious, the method would not have been patented.

In conclusion, the priority applications listed by Applicants do not provide support for the claimed RCA amplification and detection method. The rejection over Fan et al. is maintained.

B) Regarding rejection of claims 27-41 under 35 U.S.C. 103(a) over Taylor and Walt et al., Applicants argue that there is no motivation to combine these two references, because:

a) Walt et al. do not suggest using probe amplification schemes in conjunction with microspheres (page 27 of the amendment, second paragraph).

b) Examiner used hindsight reasoning to combine the references without additional support "that the prior art would have suggested, motivated or taught one of ordinary skill to make the claimed combination.." (page 29 of the amendment, second paragraph).

c) Taylor, which was filed two years after the filing date of Walt et al., "is silent as to the combination of an amplification scheme in conjunction with use of microspheres as an additional step or component in the array detection method". Further, Applicants state that Taylor would have known Walt et al. references, since they were published before the filing date of his application.

d) Finally, Applicants conclude "The Office Action neither cites art showing a combination of microspheres with a probe amplification scheme nor cites to text in the cited references that provide a suggestion, motivation or teaching to combine rolling circle amplification scheme with microsphere components of an array to achieve the claimed combination. The alleged rational fails to support any motivation because there is no evidence that the arrays of Taylor did not support a

large number of functionalities or were difficult to produce or use." (page 30 of the amendment, second paragraph).

Regarding a), Walt et al. teach a general method of detection of different analytes, including nucleic acids (Table V; col. 10, lines 4-16), on microbead-based arrays, by capturing target sequences with capture probes bound to microspheres. Therefore, Walt et al. teach detection of nucleic acids by capture onto a microbead array with capture probes attached to microbeads, therefore such detection method can be applied to any process in which detection of nucleic acids is desired, such as detection of amplification products.

Regarding c), Taylor specifically teaches, as Applicants have put it, "combination of an amplification scheme in conjunction with use of microspheres as an additional step or component in the array detection method". For example, in paragraph [0003], Taylor teaches

"In general, the invention includes <u>methods which combine isothermal methods of nucleic acid amplification with a positional array analysis</u>. In some embodiments, the array is a three dimensional array, e.g., a gel pad array, analysis. In preferred methods, a target is isothermally amplified, and the amplification product is contacted with a positional array, thereby analyzing a nucleic acid sequence. Examples of isothermal amplification include, rolling circle amplification, nucleic acid sequence-based amplification (NASBA) (see, e.g., U.S. Pat. Nos. 5,409,818 and 5,130,238), self sustained sequence replication (3SR), strand displacement amplification (SDA) (see, e.g., U.S. Pat. Nos. 5,523,204; 5,455,166; 5,631,147; 5,712,124, and 5,733,752), cycling probe reaction or TMA, (see, e.g., U.S. Pat. Nos. 5,554,516; 5,480,784; and 5,399,491)." (emphasis added).

Further, in paragraphs [0052] and [0053], Taylor teaches

[0052] The selected population of circular sequences is amplified by rolling circle application. The amplified population of sequences from the said rolling circle amplification, e.g., can be amplified further. For example, it can be amplified by rolling circle amplification. The second or subsequent amplifications can be done prior to further analysis. The subsequent rolling circle amplifications can use the same or similar circular sequence as was used in the initial R.C.A. or a different circular sequence. It is also possible that the circular sequence can be, for example, from a closed or open circular template.

[0053] Amplified circles, or cleavage products thereof are applied to an array of a plurality of capture probes, wherein each of the capture probes is positionally distinguishable from other capture probes of the plurality on the array, and wherein each positionally distinguishable capture probe includes a unique (i.e., not repeated in another capture probe) region complementary to the plurality of selector probes;

[0054] hybridizing the amplified sample sequence with the array of capture probes, thereby identifying circular nucleotide sequences that bind to and/or alter the function of proteins or other targets." (emphasis added).

Furthermore, Taylor teaches that cleaved RCA products can be attached to microbeads, and analyzed on a Cantor-type array (U.S. Patent No. 5,503,980). Investigation of the Cantor patent reveals that Cantor-type array is in fact a microbead array, with capture probes attached to microbeads (see, for example, Examples 1 and 13). Therefore, Taylor provides specific connection not only between detection of amplification products on an array, but specifically for the detection of RCA amplification products on a microbead array.

Therefore, regarding b), no hindsight was necessary to combine the two references. Taylor provides a method of detection of RCA amplification product on arrays, including microbead

arrays, whereas Walt et al. teach microbead arrays which are useful in a detection of a wide range of analytes, including nucleic acids. Both references teach microbeads, and Walt et al. teaches an efficient and inexpensive way of creating an array (col. 3, lines 26-30). Therefore, provided with the teachings of Taylor and Walt et al., a skilled artisan would be motivated to use the microbead array of Walt et al. to detect the microbead amplification products of Taylor.

Regarding d), there is no evidence that the arrays would have been easy to produce and use. Furthermore, the following statement of Walt et al. further supports the motivation to use a microbead array: "Although each sensor is different insofar that it has a different distribution of the subpopulations of beads within its wells, only those beads that exhibit a positive optical response or signature change need to be decoded. Therefore, the burden is placed on the analysis rather than on sensor manufacture. Moreover, since the beads and fibers in the array can be monodisperse, the fluorescent regions arising from signal generation are extremely uniform and can be analyzed automatically using commercially available microscopy analysis software, such image processing software is capable of defining different spectral regions automatically and counting the number of segments within each region in several seconds.", as providing inexpensive and easy to use detection tool.

The rejection is maintained.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an

application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 27-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Fan et al. (Publication US 2002/0006617 A1; cited in the previous office action).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claims 27 and 43, Fan et al. teach a genotyping assay based on rolling circle amplification (RCA). A single target probe (RCA probe or padlock probe) is hybridized with a target nucleic acid, with each terminus of the probe hybridizing to adjacent portions of the target. The probe is circularized by ligation and amplified in the presence of a polymerase and a primer. The first end of the probe is substantially complementary to a first target domain and the second end is substantially complementary to a second target domain, which is adjacent to the first target domain ([0091], [0094], [0100]).

The probe contains a restriction site, which allows cleavage of the concatamers resulting from RCA amplification. Concatamers are cleaved into smaller fragments, which are then contacted with capture probes immobilized on microspheres (= beads). The capture probes on microspheres form an array. The digested fragments can be detected in two ways: either labeled nucleotides are incorporated during the amplification step or an additional labeled probe can be used ([0098], [0102]).

Fan et al. teach ordered and random arrays ([0152], [0179], [0180]). Microspheres are distributed in discrete sites on a substrate ([0156]- [0162]).

Regarding claims 28, 29, 41 and 42, Fan et al. teach that the first and second target domains may be directly adjacent or separated by one or more nucleotides, in which case a polymerase and dNTPs are used to fill the gap. The target domain orientation (5' or 3') depends on the orientation of the complementary target sequence ([0031]). Fan et al. teach ligases ([0114], [0295]). Regarding claim 30, Fan et al. teach a polymerase ([0091],[0304]).

Regarding claim 31, Fan et al. teach labeled nucleotides in the amplification reaction ([0095]).

Regarding claim 32, Fan et al. teach contacting concatamer with a restriction enzyme ([0098], [0102]).

Regarding claim 33, Fan et al. teach wells ([0157]).

Regarding claim 34, Fan et al. teach a fiber optic bundle as a substrate ([0156]).

Regarding claim 35, Fan et al. teach substrates being glass or plastic ([0154]).

Regarding claim 36, Fan et al. teach random distribution of microspheres on the array ([0179], [0180]).

Regarding claim 37, Fan et al. teach the RCA probe comprising an adapter sequence ([0097]).

Regarding claim 38, Fan et al. teach the RCA probe containing a restriction site ([0098]).

Regarding claim 39, Fan et al. teach an RCA probe comprising a first and second target specific portions ([0096]), an amplification priming site ([0100]), an adapter sequence ([0097]) and a restriction site ([0098]).

Regarding claim 40, Fan et al. teach adapter sequences complementary to capture probes ([0022]).

Regarding claim 43, Fan et al. teach immobilization of the target nucleic acid either before or after formation of the hybridization complex (page 9, [0078]).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 27-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (Publication No. US 2002/0168645 A1) and Walt et al. (U.S. Patent No. 6,023,540).

A) Regarding claims 27, 28, 30, 41 and 43, Taylor teaches detection of nucleic acid using rolling circle amplification. The method comprises hybridizing a single-stranded circular template (= circularized probe) to a sample (= target) nucleic acid, where the circular template has at least one sequence complementary to the target and at least one oligonucleotide which results in a cleavage site in an oligonucleotide multimer (= concatamer), followed by addition of a primer, dNTPs and a polymerase to produce an oligonucleotide multimer, cleavage of the multimer to produce cleaved amplified nucleic acid (= amplicon cleavage products), and contacting the cleavage products with an array of capture probes to detect the amplification products ([0005]-[0011], [0121]).

The circularized probe is prepared by hybridizing each end of a linear oligonucleotide (= circular primer) to a sample sequence, in such a way that a 3' end of the linear oligonucleotide has a sequence complementary to the 5' end of the target and the 5' end of the linear oligonucleotide has

a sequence complementary to the 3' end of the target, and the 5' and 3' ends of the linear oligonucleotide are immediately adjacent to each other, followed by joining the ends of the linear oligonucleotide to form a circularized probe ([0012]-[0014]).

Taylor teaches an extension reaction catalyzed by a polymerase, a linking reaction catalyzed by a ligase and a nucleic acid cleavage reaction catalyzed by a restriction enzyme ([0036]).

Regarding claims 29 and 37-40, Taylor teaches an RCA probe with an interrogation region at its 5' end, which is complementary to an interrogation sequence (= detection position) on the target, and a terminal sequence at its 3' end, complementary to the probe annealing sequence of the target (Fig. 1; [0153-0156], [0164]). The interrogation sequence may contain a polymorphic region, such as a single nucleotide polymorphism (SNP). The interrogation sequence can be positioned at the 3' end of the probe ([0168]). Taylor teaches an RCA probe comprising a restriction endonuclease site ([0159], Fig. 1), a tag sequence (= adapter), which can be used to hybridize the amplified product to a capture probe on the array ([0161], [0162], Fig. 1), and an RCA primer sequence (= amplification priming site), which allows priming of rolling circle amplification ([0163], Fig. 1).

Regarding claim 31, Taylor teaches RCA amplification with labeled nucleotides ([0169]).

Regarding claim 32, Taylor teaches cleavage of the concatamer amplicon with a type II S restriction endonuclease ([0170]).

Regarding claim 33, Taylor teaches arrays on microtiter plates with wells ([0121]).

Regarding claim 35, Taylor teaches substrate of glass or plastic ([0122]).

Regarding claim 43, Taylor teaches target nucleic acid attached to solid support via capture probe (page 2, [0021]-[0023]).

B) Taylor does not teach capture probes attached to microspheres which are randomly distributed on a surface of a substrate, or a substrate being a fiber optic bundle.

C) Regarding claims 27, 34 and 36, Walt et al. teach a microsphere-based analytical system with microspheres carrying different chemical functionalities and positioned in wells of a fiber optic bundle sensor. The population of beads includes separate subpopulations carrying different chemical functionalities (Col. 3, lines 18-31; col. 4, lines 4-15). The microbeads are randomly distributed in an array (col. 4, lines 9-14). Each microsphere subpopulation contains different reporter dye, which may be fluorescent (col. 5, lines 40-52). The functionalites attached to the microspheres can be oligonucleotide probes (capture probes) (col. 10, lines 4-17, Table V).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the nucleic acid detection methods of Taylor on an array of Walt et al. The motivation to do so, provided by Walt et al., would have been that fiber-optic sensor supported a large number of chemical functionalities and was easy to use and manufacture.

9. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor and Walt et al. as applied to claim 27 above, and further in view of Lizardi (U.S. Patent No. 5,854,033; cited in the IDS).

A) Claim 42 is drawn to the circular primer hybridizing to target nucleic acid in such a way that it's 5' end and 3' end are not immediately adjacent and contacting the hybridization complex with a polymerase which fills the gap between the two ends of the primer.

B) Taylor teaches a probe which has the 5' and 3' ends immediately adjacent to each other upon binding to the target, but does not teach a gap between the ends of the probe.

C) Lizardi teaches an open circle probe which can bind to the target nucleic acid in such a way that it's 5' and 3' ends are separated by a gap, which can then be filled by a polymerase (col. 5, lines 25-28; col. 6, lines 39-46; Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used a probe of Lizardi in the combined method of Taylor and Walt et al. The motivation to do so, provided by Lizardi, would have been that using gaps between the ends of the probe allowed amplification of different allelic variants of the target sequence.

10. No claims are allowed.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

The examiner will move to the new office in Alexandria on January 8, 2004. The new phone number in that office is (571) 272-0789. Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
December 15, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER